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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,530	02/05/2004	George N. Cox III	4152-1-PUS-9	7322

22442 7590 05/10/2007  
SHERIDAN ROSS PC  
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EXAMINER

LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
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1648

MAIL DATE	DELIVERY MODE
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05/10/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/773,530	COX, GEORGE N.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 28 February 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 25 and 44-46 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 25 and 44-46 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date. _____   | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. Claims 25 and 44-46 are pending and under consideration in the application.
2. In the prior action, claims 24-46 were pending in the application; with claims 24 and 26-43 withdrawn, and claims 25 and 44-46 rejected. In the Response of February 28, 2007, the Applicant amended claims 44-46; and cancelled withdrawn claims 24 and 26-43.

#### ***Priority***

3. Applicant is requested to update the priority information of page 1 of the application to indicate that parent application 10/400377 has been issued as U.S. Patent 7,148,333.

#### ***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 25 and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Braxton (U.S. 5,766,897) in view of the teachings of Boissel et al. (J Biol Chem 268:15983-93), Weich et al. (Exp Hematol 21: 647-55), and Lin et al. (PNAS 82: 7580-7584). Applicant traverses the rejection on two grounds. In each case, the Applicant asserts that there is sufficient uncertainty in the art that those of ordinary skill in the art would not have had a reasonable expectation of success in the making of the claimed cysteine variant of EPO. First, the Applicant

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argues uncertainty as to the requirement for the C-terminal region of EPO for its activity.

Second, the Applicant asserts uncertainty in the making of cysteine-modified proteins. These arguments are not found persuasive.

With respect to the first argument, the Applicant points to several references showing conflicting teachings regarding the requirement for the C-terminal residues for a functional EPO protein. However, as asserted by the Applicant, the effects seen from one type of modification does not necessarily correspond to the results seen with another. Remarks, page 5, second full paragraph. Thus, while the references cited by the Applicant indicating that the deletion of the C-terminal residues may inactivate the protein, and would therefore indicate that those of ordinary skill in the art may not have had a reasonable expectation of success in the making of such deletion mutants, these teachings are sufficient to indicate that such an expectation would be absent in the present case.

This is because the present claims read on the addition of a cysteine to the C-terminal end of the protein, not a substitution of the cysteine for C-terminal residues of EPO. Such a modification would be more akin to a fusion of EPO with another protein at its C-terminus than a substitution or deletion mutant. Three instances of such EPO fusions were found in the prior art. Two of these result in an active EPO protein. See e.g., Weich, page 650 right column, and pages 651 and 653 (cited in the prior action); and Mele et al., U.S. 5,916,773, claim 1 and columns 6-8. It is noted that an earlier teaching of an EPO/ $\beta$ -galactosidase fusion did not comprise an active EPO. Nielson et al., J Immunol Methods 111: 1-9, abstract. However, the reference suggests that while fusion may have been the cause of the inactivity, so may the extreme denaturing conditions used to extract the fusion protein. Page 8. In view of the later teachings of Weich and Mele,

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those in the art would have accepted the references first explanation as to why the EPO in the fusion was inactive (i.e. the purification conditions). Thus, those in the art would have had a reasonable expectation of success in the addition of sequences or structures to the C-terminal region of the protein. The first argument is traversal is therefore not found persuasive.

The Applicant next provides arguments relating to the general unpredictability of the affects of adding cysteine residues to proteins. However, both this problem, and the requirement for the C7-C161 bridge in EPO were known in the art at the time the present application was filed as can be seen by the dates of the references relied on by the Applicant. It is noted that the requirement of the EPO bridge was also discussed in the teachings of Boissel (JBC 268:15983 at 15990). With respect to the uncertainty of the effects of additional cysteines, it is noted that other teachings in the prior art relating to the insertion of free cysteine residues (i.e. residues not in a di-sulfide bond) provide teachings relating to the refolding of such cysteine-added proteins so as to overcome the problems of adding such free cysteines. See e.g., WO 94/22466, pages 12-13, and 16-18; and WO 94/12219, pages 16-17 ( both references of record in the November 2005 IDS). Moreover, it is also noted that there are no additional teachings in the present application as to any other means for avoiding such potentially detrimental effects of adding the extra cysteine. Thus, the teachings in the prior art appear to adequately enable those of ordinary skill in the art to make the claims cysteine modified proteins. The Applicant's argument relating to the general uncertainty of the effects of adding free-cysteines is therefore also not found persuasive.

Applicant's submission of the Declaration by George Cox is noted. However, as the declaration does no more than indicate that an embodiment of the claimed cysteine variants has been produced, and provides no evidence or argument relating to the propriety of the rejection,

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the declaration is not found persuasive in establishing the non-obviousness of the claimed invention.

The rejection is therefore maintained for the reasons above and the reasons of record.

### ***Conclusion***

6. No claims are allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

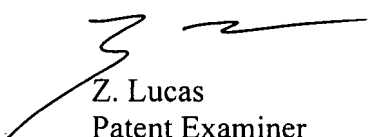
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Z. Lucas  
Patent Examiner